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EXAMINER

RAWLINGS, STEPHEN L

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1642

DATE MAILED: 05/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/807,355	Applicant(s) DERVAN, PETER B.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 February 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>20011010; 20021122</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. The election with traverse filed February 3, 2004 is acknowledged and has been entered. Applicant has elected the invention of group I, claims 1-24, insofar as the claims are drawn to a composition suitable to inhibit the transcription of an oncogene by modulating the binding to double stranded DNA of ESX and a method for treating a subject comprising administering to said subject said composition, wherein said composition comprises at least one polyamide, wherein said at least one polyamide is Her2-1.
2. Claims 1-24 are pending in the application.
3. Claims 1-24, insofar as the claims are drawn to the elected invention, are currently under prosecution.

Election/Restrictions

4. Applicant has traversed the restriction and election requirement set forth in the Office action mailed October 3, 2003 arguing the restriction is improper because a search could be formulated such that the entire application could be examined without serious burden.

Applicant's argument has been carefully considered but not found persuasive. The search that is required to examine any one of the inventions is not the same as, or co-extensive with the search that would be required to examine any other invention. Accordingly, an additional and different search would have to be performed to examine each additional invention, which need would constitute a serious burden. Therefore, the requirement and election requirement is deemed proper and made FINAL.

Information Disclosure Statement

5. The information disclosures filed October 10, 2001 and November 22, 2002 have been considered. An initialed copy of each is enclosed.

Sequence Rules Compliance

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be further examined under 35 U.S.C. §§ 131 and 132.

Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). In this instance, as noted on the attached Notice to Comply, sequences are depicted in Figures 1 and 3, which are not properly identified by sequence identification numbers but which are of sufficient length to fall under the requirements set forth under 37 CFR §§ 1.821-1.825. As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. Sequence identifiers for sequences appearing in the drawings may appear in the Brief Description of the Drawings. Applicant must provide appropriate amendments to the specification or drawings inserting the required sequence identifiers. If the amendments are extensive then a substitute specification may be required.

Applicant is given the same period of time within which to reply to this Office action to comply with the sequence rules under 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g).

Specification

7. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks

should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of improperly demarcated trademarks include the following: Adriamycin™ (page 18, line 7); RNAzol™ (page 21, lines 11, and page 22, line 18); and Phosphorimager™ (page 21, line 14, and page 23, line 19).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at <http://www.uspto.gov/web/menu/search.html>.

8. The specification is objected to because at page 1 it recites: "This application claims benefit of priority from U.S. Provisional Application 60/099,906". As the provisional application expired one year after its filing date, the provisional application was not copending when the instant application was filed. Accordingly, it is improper to claim direct benefit of the earlier filing date of the provisional application. Nevertheless, as the instant application was filed under 35 USC § 371 as the national stage entry of PCT/US99/20971, which properly claimed benefit of US Provisional Application No. 60/099,906, the instant application enjoys benefit of the earlier filing date of the provisional application. Appropriate correction is required; e.g., amending the first line of the specification to recite the full priority claim.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

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which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-12 and 24 are drawn to a composition for treating a subject having a condition associated with expression or overexpression of an oncogene, which comprises a polyamide-nucleic acid molecule. Claims 13-24 are drawn to a method of treatment comprising administering to a subject having a condition associated with expression or overexpression of an oncogene such a composition comprising a polyamide-nucleic acid molecule.

Accordingly, the claims encompass a genus of compositions comprising a genus of polyamide-nucleic acid molecules. The members of the genus of polyamide-nucleic acid molecules have the common functional feature of inhibiting the transcription of some gene. Notably the claims do not expressly require the members of the genus to inhibit the transcription of the oncogene that is expressed or overexpressed in the subject's cells. Therefore, the members of the genus of polyamide-nucleic acid molecules of which the claimed compositions are comprised include any polyamide-nucleic acid molecule capable of inhibiting the transcription of some gene, whether the gene be known or yet to be discovered. Even if the claimed genus of compositions were limited to compositions comprising a polyamide-nucleic acid molecule capable of inhibiting the transcription of an oncogene, notably the genes would encompass compositions comprising polyamide-nucleic acid molecules capable of inhibiting every known oncogene, as well as any oncogene that has yet to be discovered.

Although the members of the genus of polyamide-nucleic acid molecules have the common feature of inhibiting the transcription of some gene, the members of the genus must necessarily have widely varying structures. The structures of the members of the genus of polyamide-nucleic acid molecules must necessarily vary to selectively target and inhibit the transcription of every known, or yet to be discovered gene; and there is no correlation between structure and function, which might serve to describe at least a substantial number of the members of the genus of polyamide-nucleic acid molecules of which the claimed members of the genus of compositions is comprised,

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such that the skilled artisan would immediately recognize that at least a substantial number of the members of the claimed genus of compositions were actually in Applicant's possession at the time the application was filed. By the same token, Applicant's disclosure of the claimed invention would not reasonably convey to the skilled artisan that Applicant was in possession of the claimed methods of treatment, which comprise administering the members of the claimed genus of compositions, at the time the application was filed.

Furthermore, because the structure of any yet to be discovered gene cannot be known, even given benefit of Applicant's disclosure, the skilled artisan could not possibly envision the structure of the polyamide-nucleic acid molecule of which the claimed composition is comprised, which can be used to inhibit the transcription of that gene. Moreover, since the skilled artisan cannot predict which transcription factors, e.g., ESX, might be involved in regulating the transcription of a yet to be discovered gene, even given the benefit of Applicant's disclosure, the skilled artisan could not recognize whether the transcription of such a gene might be inhibited by a polyamide-nucleic acid molecule that commonly inhibits the transcription of various other genes comprising a common promoter element to which a common transcription factor, e.g., ESX, binds. Because the skilled artisan could not recognize whether any given polyamide-nucleic acid molecule might inhibit the transcription of any given gene, the skilled artisan could not distinguish the members of the claimed genus of compositions, or methods, from others.

In addition, while the specification describes a few promoter elements of which the promoter of the gene *HER2* is comprised in Figure 1, for example, the skilled artisan would not reasonably regard the promoter of *HER2* as representative of the structure of at least a substantial number of the promoters of other known oncogenes. The skilled artisan appreciates that while the promoters of genes transcribed by RNA polymerase II have some common features, e.g., most of such comprise a TATA box, there are countless differences. The transcription of genes is regulated by a variety of different transcription factors binding different promoter elements having unique polynucleotide sequences. Consequently, only a small fraction of the known oncogenes comprise

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promoters, which are regulated by ESX; and only those oncogenes known to be regulated by ESX, or disclosed as being regulated by ESX, and which comprise the same ESX binding element, might reasonably be recognized by the skilled artisan as potential targets for therapy using the disclosed polyamide-nucleic acid molecules, which Applicant shows are capable of inhibiting the transcription of *HER2*. However, the only disclosed oncogene comprising an ESX binding element, the transcription of which can be inhibited by the disclosed polyamide-nucleic acid molecule, is *HER2*. Absent a description, or knowledge of the structures of the promoters of other known oncogenes, even given the benefit of Applicant's disclosure, the skilled artisan could not envision the structures of other polyamide-nucleic acid molecules that might be capable of inhibiting the transcription of those oncogenes. Therefore, Applicant's disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Similarly, while the specification describes the structures of a polyamide-nucleic acid molecule, e.g., Her2-1, which can be used to inhibit the transcription of *HER2*, the skilled artisan would not reasonably regard the disclosed polyamide-nucleic acid molecules as representative of the widely varying structures of at least a substantial number of the polyamide-nucleic acid molecules of which the claimed members of the genus of compositions is comprised. The specification teaches Her2-1 was designed to bind a DNA sequence immediately upstream of the TATA box of the promoter of *HER2* (page 14, lines 3-5); and the specification discloses Her2-1 inhibits TBP binding to the TATA box and thereby inhibits transcription of the gene (page 10, lines 15-18). The specification does not disclose that Her2-1 is capable of inhibiting binding of ESX, nor is it expected that Her2-1 is capable of doing so. Accordingly, the structure of Her2-1 is not representative of the genus of polyamide-nucleic acid molecules that is capable of inhibiting the binding of ESX, or any other transcription factor, and is therefore not representative of the genus of polyamide-nucleic acid molecules capable of inhibiting the transcription of genes regulated by such other transcription factors. Moreover, the skilled artisan appreciates that because the promoters of genes transcribed by RNA polymerase II, for example, have countless differences, and moreover the transcription

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of those genes is regulated by a variety of different transcription factors binding to different promoter elements having unique polynucleotide sequences, the structures of the polyamide-nucleic acid molecules must be tailored according to the structures of those promoter elements, such that the polyamide-nucleic acid molecule binds a given promoter element to inhibit the activity of the transcription factor and thereby inhibit the transcription of the gene. MPEP § 2163.02 states, “[a]n objective standard for determining compliance with the written description requirement is, ‘does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed’ ”. The courts have decided:

The purpose of the “written description” requirement is broader than to merely explain how to “make and use”; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the “written description” inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Furthermore, in deciding *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the Court held that a generic statement that defines a genus of nucleic acids *by only their functional activity*, or more aptly in this instance, a genus of polyamide-nucleic acid molecules by a common ability to inhibit the transcription of a gene, does not provide an adequate written description of the genus. Furthermore, the Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property

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alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (*Id.* at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. The *Guidelines* further state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

Finally, as the claims are drawn to a genus of polyamide-nucleic acid molecules, which can be administered to a subject having a disease associated with the expression or overexpression of an oncogene, it is aptly noted that the disclosure appears to include only a description of breast cancer, which is associated with the overexpression of *HER2*. The disclosure does not appear to include a description of any other condition

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associated with the expression or overexpression of an oncogene that might be treated using the claimed composition or method. The disclosure of the single example of a condition, which is associated with a single example of an oncogene, does not adequately describe the claimed genus of compositions or methods of treatment, because breast cancer is not considered representative of other conditions associated with the expression or overexpression of *HER2*, or any other oncogene, such that the skilled artisan would appreciate that Applicant had possession of the claimed invention at the time the application was filed. The claims encompass compositions and methods for treating conditions, which have yet to be discovered, or which have yet to be recognized as being associated with the expression or overexpression of an oncogene.

11. Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-12 and 24 are drawn to a composition for treating a subject having a condition associated with expression or overexpression of an oncogene, which comprises a polyamide-nucleic acid molecule. Claims 13-24 are drawn to a method of treatment comprising administering to a subject having a condition associated with expression or overexpression of an oncogene such a composition comprising a polyamide-nucleic acid molecule.

Accordingly, the claims encompass a genus of compositions comprising a genus of polyamide-nucleic acid molecules, which can be administered to a subject having a disease associated with the expression or overexpression of an oncogene such that the expression of a gene, not necessarily the oncogene, is inhibited at the level of its transcription.

The specification teaches a polyamide-nucleic acid molecule, Her2-1, which inhibits binding of TBP to the TATA box of *HER2* and thereby inhibits the transcription of the oncogene; see, e.g., page 10, lines 15-18.

Her2-1 inhibits binding of TBP but there is no factual evidence showing that Her2-1 is capable of inhibiting the transcription of an oncogene by modulating the binding of other protein factors, including ESX. ESX binds a sequence that is upstream of the site that is targeted by Her2-1. Binding of Her2-1 to the TATA box is not expected to affect binding of the upstream promoter element to which ESX binds. For this reason alone the elected invention is not enabled by the specification.

Additional reasons the amount of guidance, direction, and exemplification disclosed is not sufficient to meet the enablement requirement set forth under 35 USC § 112, first paragraph include the following:

The amount of guidance, direction, and exemplification set forth in the specification would not be sufficient to enable the skilled artisan to make and use the claimed invention with a reasonable expectation of success without the need to first perform an undue amount of additional experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

Although the specification teaches the production and use of the polyamide-nucleic acid molecule, Her2-1, to inhibit binding of TBP to the promoter of *HER2* to inhibit the gene's transcription, this amount of guidance, direction, and exemplification would not be sufficient to provide the skilled artisan with a reasonable expectation of success in using the claimed invention to treat any condition associated with expression or overexpression of an oncogene. The amount of guidance and direction set forth in the specification would not be sufficient to enable the skilled artisan to design and synthesize a polyamide-nucleic acid molecule encompassed by the claims, which could be used to inhibit the transcription of any oncogene, other than *HER2*.

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Furthermore, short of empirical determination, the skilled artisan cannot accurately and reliably predict whether a polyamide-nucleic acid molecule, which has been designed to target the promoter of a particular oncogene, can be used effectively to inhibit the transcription of the oncogene. As the specification discloses at page 9, lines 22-28, the polyamide-nucleic acid molecule must be designed with the knowledge of which sequence should be targeted and how the transcription factor binds the targeted sequence. For example, the specification discloses, if the transcription factor binds in the major groove, the polyamide-nucleic acid molecule must bind the DNA molecule in a manner that induces a conformational change in the DNA molecule, such that the transcription factor does not recognize its former binding site. While it is possible to design a polyamide-nucleic acid molecule to bind a particular DNA sequence, it is not possible to predict whether binding of the polyamide-nucleic acid molecule will induce a conformational change in the DNA molecule, which prevents binding of a major groove binding transcription factor to inhibit the transcription of a targeted gene.

Even limiting the scope of the claims to a composition and method for treatment of breast cancer, and limiting the claimed composition to a composition comprising Her2-1, the skilled artisan could not have a reasonable expectation of successfully using the claimed invention without the need to first perform an undue amount of additional experimentation. One cannot extrapolate the teachings of the specification to the enablement of the invention, particularly in the absence of exemplification, because it is well known that the art of drug discovery for is highly unpredictable. With regard to anticancer drug discovery, for example, Gura (*Science* **278**: 1041-1042, 1997) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs). Moreover, because of the lack of predictability in the art, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal

or cell that has been used as a model, but which is ineffective in humans, indicating that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2).

Although the teachings of Bergers et al. (*Current Opinion in Genetics and Development* **10**: 120-127, 2000) are drawn to specific antitumor agents, namely matrix metalloproteinase inhibitors, the great extent of unpredictability in the art is underscored by the disclosures of Berger et al. Bergers et al. teaches, "a body of data over the past few years indicate [...] that proteinases and proteinase inhibitors may, under special circumstance, either favor or block tumor progression. For example, ectopic expression of TIMP-1 [a natural inhibitor of metalloproteinases] allows for some tumors to grow, while inhibiting others" (page 125, column 2). In fact, Bergers et al. discloses the Bayer Corporation recently halted a clinical trial of a metalloproteinase inhibitor because patients given the drug experienced greater progression of cancer than did patients given a placebo (page 125, column 1). Bergers et al. comments, "these results are somewhat surprising and contrary to Bayers' preclinical data, which confirmed that the drug inhibited tumor activity in rodents" (page 124, columns 1-2). Bergers et al. also teaches that the absence of a metalloproteinase activity in mice actually predisposes the mice to *de novo* squamous carcinomas. Thus, it is relatively clear that one skilled in the art cannot predict the effect of administering a pharmaceutical composition purported to have a desired pharmacological effect to a subject, despite some hypothetical conjecture or even preclinical evidence that it might be used to treat the targeted condition or disease. Always the efficacy of any unproven drug must be determined empirically. Therefore, in such an unpredictable art as this, the disclosure of such empirical determinations (i.e., working exemplification) must be commensurate in scope with its expected and indicated uses, if the specification is to be considered enabling; otherwise, in the absence of sufficient exemplification, the skilled artisan would have to perform an undue amount of additional experimentation to have a reasonable expectation of success in practicing the claimed invention with such therapeutic objective.

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Although a polyamide-nucleic acid molecule encompassed by the claims might bind DNA to inhibit the binding of a transcription factor, one cannot always predict whether inhibiting the binding of a given transcription factor will result in an inhibition of transcription of the gene regulated by the transcription factor. It may prove insufficient to modulate the binding of a single given transcription factor to effectively inhibit transcription of a given gene. Although some transcription factors upregulate transcription of a given gene, the transcription factor is generally not absolutely essential, since transcription of genes are controlled by a several different transcription factors. For example, the specification discloses the expression of *HER2* at the level of transcription is regulated by at least three different transcription factors, TBP/TFIID, ESX, and NF-Y, and possibly others, including PEA3 and ERM (Figure 1). Apart from possibly TBP, none of the transcription factors is essential. Hurst (*Breast Cancer Res.* 3: 395-398, 2001) reviews the current understanding of the *ERBB2*, i.e., *HER2*, promoter; see, e.g., the abstract. Hurst teaches a number of transcription factors have been demonstrated to bind the proximal promoter of *HER2*, including members of the AP-2 and Ets families of transcription factors (page 396, column 2). Hurst teaches that while AP-2, for example, has been shown to be required for maximal promoter activity and associated with overexpression of the gene in breast cancer, mutation of its DNA binding site to prevent its binding to the promoter impairs the transcription activity of the promoter but does not abolish the activity (page 396, column 2).

The claimed invention is specifically drawn to a composition comprising a polyamide-nucleic acid molecule that modulates the binding of ESX, but Hurst (cited *supra*) also teaches that while other Ets family members have been shown to bind and regulate transcription of *HER2*, only PEA3 has so far been shown to correlate in distribution with the overexpression of the gene (page 397, column 1). Consequently as the claimed invention is specifically drawn to a composition comprising a polyamide-nucleic acid molecule that modulates the binding of ESX, because PEA3 appears to be the key regulator of *HER2* overexpression, inhibiting binding of ESX, rather than PEA3, may not be effective to inhibit the expression of the gene in overexpressing cancer cells,

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or effective to inhibit the growth of such cancer cells by effectively diminishing the level of *HER2* expression.

Furthermore, inhibiting the binding of TBP at the site targeted by Her2-1 may not be effective to inhibit the growth of such cancer cells by effectively diminishing the level of *HER2* expression, because Hurst notes the increased use by *HER2* of an alternative transcription start site at -69, rather than the TBP-binding site targeted by Her2-1, in *HER2* overexpressing cells (page 396, column 2). A cell may compensate for any inhibition of transcription from the start site targeted by Her2-1 by increasing its use of the alternative start site.

The claimed invention is specifically drawn to a composition for treating a condition associated with the expression or overexpression of an oncogene, such as *HER2*, including breast cancer and other types of cancers. Limiting the scope of the claims to a composition and method for treating cancer associated with the overexpression of *HER2*, the amount of guidance, direction, and exemplification disclosed by Applicant would still not be sufficient to meet the requirements set forth under 35 USC § 112, first paragraph, because Vernimmen et al. (*Br. J. Cancer* **89**: 899-906, 2003) teaches the promoter regions involved in *ERBB2*, i.e., *HER2*, overexpression in breast cancer cells are different from those that lead to gene upregulation in colon and ovary cancers; see, e.g., the abstract. Therefore, the skilled artisan could not have a reasonable expectation of successfully using the claimed invention to treat colon, ovary, and other types of cancer associated with the overexpression of *HER2*, because the skilled artisan cannot predict whether the claimed composition can be used to inhibit the expression of the gene to the extent that the growth of the cancer cells are adversely affected by the treatment. An undue amount of additional experimentation would be required to identify the transcription factors that mediate maximal expression of the gene in types of cancer, other than breast cancer, design polyamide-nucleic acid molecules that target the sites to which those transcription factors bind, and determine whether a composition comprising such an agent can be used effectively to inhibit the transcription of the gene in those types of cancer and thereby inhibit their growth.

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In addition, while the claimed invention encompasses a composition and method for treatment of a type of cancer associated with the expression or overexpression of an oncogene by inhibiting the transcription inducing activity of a transcription factor, such as ESX, paradoxically the treatment may promote the growth the some types of cancer, since Park et al. (*Oncogene* **20**: 1235-1245, 2001) teaches the activity of the gene encoding TGF β - type II receptor is regulated by ESX (abstract). Park et al. discloses the inactivation of the TGF β -mediated signaling pathway contributes to malignant transformation in gastric cancer and occurs through several mechanisms, including the transcriptional repression of the gene encoding TGF β - type II receptor (page 1235, column 1 through column 2). Park et al. teaches ESX binds to the promoter of the gene encoding TGF β - type II receptor and induces its activity (abstract). Therefore, in the case of gastric cancer, it cannot be predicted whether a composition comprising a polyamide-nucleic acid molecule that inhibits binding of ESX and affects the expression of both the genes encoding HER2 and TGF β - type II receptor in gastric cancer cells will have a positive or negative therapeutic effect, or whether perhaps inhibition of one gene will cancer the effect of inhibiting the other. More generally, then, administering a composition comprising a polyamide-nucleic acid molecule that inhibits binding of ESX to a promoter, such as the promoter encoding TGF β - type II receptor, may paradoxically have the opposite of the desired therapeutic effect of the treatment, depending upon the type of cancer and the anti- or pro-tumor activities of the various gene products, the expression of which the treatment affects. Additionally of concern, it is noted the general inhibition of transcription of ESX-regulated genes may affect the expression essential genes, such as housekeeping genes, which are expressed in normal cells. Because TBP, in particular, is ubiquitous and regulates the expression of most genes transcribed by RNA polymerase II, it is thought the disclosed polyamide-nucleic acid molecule, Her2-1, cannot be used unless it is specifically targeted to breast cancer cells, for example, without non-specifically targeting normal cells; yet it appears that Applicant has not provided a means for specifically targeting the composition to only, or even primarily affected cells. Furthermore, Brembeck et al. (*Oncogene* **19**: 1941-1949,

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2000) teaches ELF3, i.e., ESX, modulates the expression of genes, other than HER2, which are involved in differentiation; see, e.g., the abstract. Brembeck et al. teaches the novel discovery that ESX has a dual role in modulating genes: it suppresses the transcription of some genes, while inducing the expression of another (abstract). Thus, administering the claimed composition might inhibit the expression of an oncogene, e.g., HER2, but concomitantly result in the activation of another oncogene, the expression of which is normally repressed by ESX. Together these facts again underscores the need of the skilled artisan to first perform an undue amount of additional experimentation before having a reasonable expectation of success in using the claimed invention.

Finally, as any use of the claimed invention is in essence the application of an “antisense technology”, its use necessarily suffers the same limitations met by other applications of the technology. The art of antisense oligonucleotide-mediated therapy is not conventional, nor are the studies or methodology routine. In the abstract, Sohail et al. (*Current Opinions in Molecular Therapy* 2: 264-271, 2000) teaches:

Despite the simplicity of the concept, almost every step in an antisense experiment poses difficulties. Finding a site that is accessible to intermolecular hybridization with complementary nucleic acids is a major problem and determines the success or failure of an antisense experiment. A major determinant of accessibility appears to be the intramolecular folding in mRNAs that renders much of the molecule inaccessible. However, owing to our poor understanding of RNA folding and the mechanisms of heteroduplex formation, theoretical methods have limited use in finding accessible sites. Such methods are unable to address two major considerations when describing an antisense reagent, i.e., which is the most accessible sequence in the target and what length of the reagent works best in terms of activity and specificity. Empirical approaches appear more successful.

Also with regard to the evident lack of conventionality in the art, Pierce et al. (*Nucleic Acids Research* 26: 5093-5101, 1998) explains:

A key parameter in the success or failure of an antisense therapy is the identification of a suitable target site on the chosen mRNA. Ultimately, the accessibility of the target to the antisense agent determines target suitability. Since accessibility is a function of so many complex factors, it is currently beyond our ability to predict.

Despite the voluminous number of studies that have been performed, the many limitations of antisense therapy have yet to have been overcome. In particular, the pre-clinical application of antisense therapies have met with little success due to the inherent instability of the antisense molecules *in vivo*, which to some extent results from susceptibility to nucleases, due to the inability to effectively deliver the antisense reagents to the targeted tissues, which has wrought undesirable, adverse non-specific toxicity, and due to non-specific hybridization, which also may have undesirable effects. For example, Lesoon-Wood et al. (*Cancer Letters* **147**: 163-173, 1999) discovered that control antisense molecules, which were expected not to have an effect, caused a considerable level of non-specific inhibition of expression. Moreover, Lesoon-Wood et al. found that the control antisense molecule enhanced the neoplastic transformation of cells treated with the molecule.

To the extent that the claims are drawn to a composition and a method for the treatment of a cancer that expresses, as opposed to overexpresses, an oncogene, Roh et al. (*J. Surg. Res.* **77**: 85-90, 1998) teaches that an antisense oligonucleotide, which inhibits the transcription of HER2, has no effect on the growth of breast cancer cells that express low levels of the gene; only the growth of cells expressing high levels of the gene were affected by the treatment; see, e.g., the abstract. Similar results have been reported by Colomer et al. (*Br. J. Cancer* **70**: 819-825, 1994); see the abstract, for example. These results again underscore the need to empirically determine whether the claimed invention can be used effectively before the skilled artisan might have a reasonable expectation of success in using the claimed invention in a manner that is reasonably commensurate in scope with the claims.

In summary, the amount of guidance, direction, and exemplification is not reasonably commensurate in scope with the claims; nor would it be sufficient to enable the skilled artisan to have a reasonable expectation of success in using the claimed invention to treat a subject having a condition associated with expression or overexpression of an oncogene. Because the invention cannot be practiced with a reasonable expectation of success without the need to first perform an undue amount of

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additional experimentation, the disclosure of the claimed invention has not met the enablement requirement set forth under 35 USC § 112, first paragraph.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 6, 18, and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6 and 18 are indefinite because the claims recite, "wherein said polyamide has [...] a selectivity of at least about two". The recitation of the limitation renders the claims indefinite because the claims do not recite the standard by which the binding selectivity is measured, and it does not appear that specification provides precise guidance as to how it can be ascertained whether a given polyamide of claim 1 fulfills the requirement of the claims. Accordingly, the metes and bounds of the subject matter that Applicant regards as the invention cannot be ascertained, such that the requirements set forth under 35 USC § 112, second paragraph are met.

Claim 24 is indefinite because the claims recites: "The method of claim 1". Recitation of the limitation renders the claim indefinite because claim 1 is drawn to a composition, not a method. Accordingly, the metes and bounds of the subject matter that Applicant regards as the invention cannot be ascertained.

Conclusion

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.


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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne (Bonnie) Eyler, Ph.D. can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
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slr
April 29, 2004


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